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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/311,996 05/14/99 VAISBERG

E 19681-4

EXAMINER

022434 HM22/0214
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STH-S
ART UNIT

PAPER NUMBER

1631
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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/311,996

Applicant(s)

VAISBERG ET AL.

Examiner

Stephen Siu

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 December 2000.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-12, 19-41, 44 and 45 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12, 19-41, 44 and 45 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 6.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

DETAILED ACTION

This is in response to Applicant's Amendment received December 29, 2000
(paper number 7).

The objection to claims 37, 45 and 48 as cited in the office action mailed September 9, 2000 (paper number 3) is withdrawn in view of Applicant's amendments and arguments.

The rejection of claims 6, 7, and 40-45 under 35 U.S.C. 112, second paragraph as cited in the office action mailed September 9, 2000 (paper number 3) is withdrawn in view of Applicant's amendments and arguments.

The rejection of claims 1-5, 8-12, and 17-48 under 35 U.S.C. 102(b) as being anticipated by Pauwels (Journal of Pharmacological and Toxicological Methods, Vol.37, March 1997, pages 105-115) as cited in the office action mailed September 9, 2000 (paper number 3) is withdrawn in view of Applicant's amendments and arguments.

The rejection of claims 31 under 35 U.S.C. 103(a) as being unpatentable over Pauwels in view of Weinstein (Science, Vol.275, 17 Jan 1997, pages 343-349) as cited in the office action mailed September 9, 2000 (paper number 3) is withdrawn in view of Applicant's amendments and arguments.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 1-6 and 8-10 under 35 U.S.C. 102(b) as being anticipated by Biodx (WO 97/45730, 12/4/97, PTO-1449 reference AC) is maintained.

Biodx (WO 9745730, 12/4/97) discloses a computer-implemented method (page 12, line 3) for analyzing cells wherein cells containing reporter molecules are scanned with a fluorescence microscope, converting the optical information into digital data, and utilizing the digital data to determine the distribution, environment or activity (i.e., "determining a description") of the labeled reporter molecules in the cells (page 11, line 19 – page 12, line 1), including a computerized method for processing, displaying (page 12, lines 2-5) and storing the data (i.e. "populating a database"). Inherent in a teaching of a "computer system" is storage medium for "holding the codes". In one embodiment, the cells are in contact with wells at temperatures ranging from ambient to 37 degrees C ("a thermal factor") – page 25, lines 22-23. Indicators are added to the cells by a variety of methods including mechanical perturbation of the membrane (i.e. "a mechanical factor") – page 27, line 10. The array of cells is subject to a fluid delivery system to enable reagent delivery to the non-uniform micro-patterned array of cells (page 23, lines 1-2). In one embodiment, the array of cells is inverted so that the wells become submerged in the etched domain filled with fluid (page 31, lines 16-18) (i.e. "a gravitational factor"). Cell nuclei are labeled with a dye and incubated at 37 degrees C (page 40, lines 18-19) (i.e. "thermal factor"). Applicant has amended the claims to recite a Markush group of manipulations, however, the claims read on any member of the Markush group which are disclosed through the teachings of Biodx.

Claim Rejections - 35 USC § 103

— The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx (WO 97/45730, 12/4/97, PTO-1449 reference AC) in view of Weaver (US Pat No 4959301, 9/25/90).

Biodx (WO 9745730, 12/4/97) discloses a computer-implemented method (page 12, line 3) for analyzing cells wherein cells containing reporter molecules are scanned with a fluorescence microscope, converting the optical information into digital data, and utilizing the digital data to determine the distribution, environment or activity (i.e., "determining a description") of the labeled reporter molecules in the cells (page 11, line 19 – page 12, line 1), including a computerized method for processing, displaying (page 12, lines 2-5) and storing the data (i.e. "populating a database"). Inherent in a teaching of a "computer system" is storage medium for "holding the codes". In one embodiment, the cells are in contact with wells at temperatures ranging from ambient to 37 degrees C ("a thermal factor") – page 25, lines 22-23. Indicators are added to the cells by a variety of methods including mechanical perturbation of the membrane (i.e. "a mechanical factor") – page 27, line 10. The array of cells is subject to a fluid delivery system to enable reagent delivery to the non-uniform micro-patterned array of cells (page 23, lines

1-2). In one embodiment, the array of cells is inverted so that the wells become submerged in the etched domain filled with fluid (page 31, lines 16-18) (i.e. "a gravitational factor"). Cell nuclei are labeled with a dye and incubated at 37 degrees C (page 40, lines 18-19) (i.e. "thermal factor").

Biodx does not teach manipulation of cells with an electromagnetic factor.

Weaver (US Pat No 4959301, 9/25/90) teaches that in cases in which biological entities do not secrete molecules of interest, or secrete molecules at a less than desired rate, it is useful to cause biological entities to release cells by providing one or more external stimuli. A general method for providing stimulus to cells, vesicles, protoplasts and small multicellular organisms involves the application of an electromagnetic stimulus which results in electroporation (see, for example, Sowers and Lieber, FEBS Lett. 205: 179-184, 1986) – col. 31, lines 50-58. Measurement of biological material can be accomplished by using measurements based on optical, weighing, sedimentation, field flow sedimentation fractionation, acoustic, magnetic, electrical and thermal means. Such measurements can be based on properties such as optical properties, mass density properties, acoustic properties, magnetic properties, electrical properties and thermal properties. It is preferred to utilize measurements based on optical properties such as are measureable utilizing light scattering, light absorbance or colorimetric, fluorescence, time-delayed fluorescence, phosphorescence and chemiluminescence. Thus, useful measurement apparatus includes flow cytometry apparatus, flow-through-microfluorimetry apparatus, optical particle analyzers apparatus, fluorescence

microscopy apparatus, light microscopy apparatus, image analysis apparatus and video recording apparatus (col.33, lines 30-47).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the computer-implemented cellular analysis method of Biodx involving manipulation of cells using any of a thermal factor, gravitational factor, or mechanical factor and to further alternatively manipulate the cells with an electromagnetic factor because it is useful to cause biological entities to release cells by providing one or more external stimuli by the application of an electromagnetic stimulus which would result in electroporation as per the teachings of Weaver. Thus, one of ordinary skill in the art would have been motivated to have performed the claimed invention with a reasonable expectation of success.

Claims 1-6 and 8-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx (WO 97/45730, 12/4/97, PTO-1449 reference AC) in view of Singhvi (US pat No 5776748, 7/7/98, filed 6/6/96).

Biodx (WO 9745730, 12/4/97) discloses a computer-implemented method (page 12, line 3) for analyzing cells as described above.

Biodx does not teach manipulation of cells with a radiation factor.

Singhvi (US Pat No 5776748, 7/7/98, filed 6/6/96) discloses a method and apparatus for use in cell analysis and biology applications such as cytometry, toxicology, cell screening, etc (col.2, lines 43-50). In one embodiment in transmission spectrophotometric assays, a translucent plate is used, a source of electromagnetic

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radiation is place on one side of the plate and a detector unit on the other (col.14, lines 45-54). Singhvi teaches the treatment with electromagnetic radiation causes changes in spectrophotometric emissions, reflection or absorption of the cells that are detected (col.16, lines 18-30). Singhvi teaches that the method allows for plating of individual cells at high density and is employable in high throughput test of potentially useful treatments including radiation to assay both qualitative and quantitative changes in individual cells and allow quantitative assays as to the percentages of cells affected by any given treatment (col.16, line 65 – col.17, line 7).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the computer-implemented cellular analysis method of Biodx involving manipulation of cells using any of a thermal factor, gravitational factor, or mechanical factor and to further alternatively manipulate the cells with an electromagnetic factor or nuclear radiation factor because doing so would allow for plating of individual cells at high density and would be useful in high throughput tests of potentially useful treatments including radiation as per the teachings of Singhvi. Thus, one of ordinary skill in the art would have been motivated to perform the claimed invention with a reasonable expectation of success.

Claims 1-6, 8-12, 17-30, 32-41, 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx in view of Weaver or Biodx and Singhvi as applied to claims 1-6 and 8-10 above, and further in view of Pauwels (Journal of Pharmacological and Toxicological Methods, Vol.37, March 1997, pages 105-115, PTO reference AE).

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Biodx and Weaver or Biodx and Singhvi disclose a computer-implemented method (page 12, line 3) for analyzing cells as described above but do not teach manipulation of cells with a chemical factor, biological factor or the precise nature of the "properties" of the manipulation.

Pauwels (Journal of Pharmacological and Toxicological Methods, Vol.37, March 1997, pages 105-115) teaches a method comprising exposing neoplastic cell lines with drugs of various pharmacological classes (i.e., "manipulating cells in various stages of the cell cycle"), monitoring drug-induced modifications by means of a digital cell image analysis of stained nuclei (i.e., "capturing an image") to create databases (page 106, col.1, lines 4-6), submitting numerical data quantitatively describing chromatin patterns to multivariate analysis with canonical transformation of the data (i.e., determining a "descriptor" from the image and populating a database) – see abstract. In the image analysis, parameters are derived including mean optical density, variance, skewness and kurtosis indices, etc. for analysis of chromatin (page 107, col.2, paragraphs 3 and 4). Inherent in a computer is a computer readable storage medium for "holding the codes". The method involves analysis of mechanism of action of anticancer drugs on neoplastic cell lines (i.e., properties comprise "applying a chemical factor", "applying a biological factor", "toxicity", "specificity against a subset of tumors", "mechanism of chemical activity", "mechanism of biological activity", "a mechanism of action", "a structure", "at least one of a plurality of adverse biological effects", "at least one of a plurality of adverse biological pathways", "at least one of a plurality of adverse clinical effects", "at least one of a plurality of cellular availability", "at least one of a plurality of

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pharmacological properties", "pharmacodynamic properties", or "selected from clinical uses and indications, human and veterinary diagnostic uses and tests, or human and veterinary prognostic uses and tests" and "manipulation" comprising "a temporal factor" or "applying a nuclear factor" (chromatin)).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the computer-implemented cellular analysis method of Biodx and Weaver or Biodx and Singhvi involving manipulation of cells using any of a thermal factor, gravitational factor, mechanical factor, electromagnetic factor or radiation factor and to further manipulate the cells with a manipulations with properties comprising "applying a chemical factor", "applying a biological factor", "toxicity", "specificity against a subset of tumors", "mechanism of chemical activity", "mechanism of biological activity", "a mechanism of action", "a structure", "at least one of a plurality of adverse biological effects", "at least one of a plurality of adverse biological pathways", "at least one of a plurality of adverse clinical effects", "at least one of a plurality of cellular availability", "at least one of a plurality of pharmacological properties", "pharmacodynamic properties", or "selected from clinical uses and indications, human and veterinary diagnostic uses and tests, or human and veterinary prognostic uses and tests" because doing so would provide information on analysis of mechanism of action of anticancer drugs on neoplastic cell lines as per the teachings of Pauwels. Thus, one of ordinary skill in the art would have been motivated to perform the claimed invention with a reasonable expectation of success.

Claims 1-6, 8-12, 17-41, 44 and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Biodx, Weaver and Pauwels or Biodx, Singhvi and Pauwels as applied to claims 1-6, 8-12, 17-30, 32-41, ~~44~~ and 45 above, and further in view of Weinstein (Science, Vol.275, 17 Jan 1997, pages 343-349, PTO-1449 reference AJ).

Biodx, Weaver and Pauwels or Biodx, Singhvi and Pauwels disclose a computer-implemented method (page 12, line 3) for analyzing cells as described above.

Biodx, Weaver and Pauwels or Biodx, Singhvi and Pauwels do not teach the use of a gene expression profile.

Weinstein teaches the use of a gene expression profile in screening a panel of cancer cell lines.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to perform the computer-implemented cellular analysis method of Biodx, Weaver and Pauwels or Biodx, Singhvi and Pauwels involving manipulation of cells as described above and to further analyze gene expression profiles as effects on cells by external stimuli because doing so would have provided information useful in generating clinically active agents as per the teachings of Weinstein. Thus, one of ordinary skill in the art would have been motivated to perform the invention as claimed with a reasonable expectation of success.

Conclusion

No claims allowed.

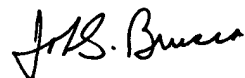
Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Stephen Siu, whose telephone number is (703) 308-

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7522. The Examiner can normally be reached from 7:00 a.m. to 3:30 p.m. on weekdays. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028. Papers related to this application may be submitted to Art Unit 1631 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. The Fax number is (703) 308-0294. Please call the Examiner at (703) 308-7522 before the transmission to expedite delivery of the fax. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Stephen Siu



JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER